

# 25 Asthma

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## Key points

- Asthma is a common and chronic inflammatory condition of the airways whose cause is not completely understood.
- Common symptoms are caused by hyperresponsive airways and include coughing, wheezing, chest tightness and shortness of breath.
- The only reliable, simple and objective way to diagnose asthma is to demonstrate reversible airflow limitation.
- In the UK, there are approximately 1400 deaths from asthma each year.
- Asthma is still a poorly controlled disease despite effective treatments.
- Asthma triggers should be avoided or controlled.
- Pharmacological therapy should involve early anti-inflammatory treatment in all but the mildest asthmatics and follow national, evidence-based guidance.
- Optimum treatment involves the lowest doses of therapy that provide good symptom control with minimal or no side effects, and the best drug delivery device is one that the patient can use correctly.
- Patients should be encouraged and educated to take an active role in their disease management, be given individualised self-management plans and be regularly supervised by the health care team.

Asthma means 'laboured breathing' in Greek and was first described 3000 years ago. It is a broad term used to refer to a disorder of the respiratory system that leads to episodic difficulty in breathing. The national UK guidelines (BTS/SIGN, 2009) define asthma as 'a chronic inflammatory disorder of the airways which occurs in susceptible individuals; inflammatory symptoms are usually associated with widespread but variable airflow obstruction and an increase in airway response to a variety of stimuli. Obstruction is often reversible either spontaneously or with treatment'.

## Epidemiology

The exact prevalence of asthma remains uncertain because of the differing ways in which airway restriction is reported, diagnostic uncertainty (especially for children under 2 years) and the overlap with other conditions such as chronic obstructive pulmonary disease (COPD). Over 5 million people in the

UK have asthma (Asthma UK, 2001) and around 300 million worldwide. Mortality from asthma is estimated at approximately 0.4 per 100,000 with around 1400 deaths per annum in the UK. Most deaths occur outside hospital; the most common reasons for death are thought to be inadequate assessment of the severity of airway obstruction by the patient and/or clinician and inadequate therapy with inhaled or oral steroids.

The probability of children having asthma-like symptoms is estimated to be between 5% and 12%, with a higher occurrence in boys than girls and in children whose parents have an allergic disorder. Between 30% and 70% of children will become symptom free by adulthood. Individuals who develop asthma at an early age, however, do have a poorer prognosis.

The prevalence of asthma actually appears to be rising despite advances in therapy. There is some doubt about this, however, due to the differing criteria for the diagnosis of asthma used in different studies. Asthma is considered to be one of the consequences of Western civilisation and appears to be related to a number of environmental factors. Air pollution resulting from industrial sources and transport may be interacting with smoking, dietary and other factors to increase the incidence of this debilitating problem.

## Aetiology

The two main causes of asthma symptoms are airway hyperresponsiveness and bronchoconstriction. Hyperresponsiveness is an increased tendency of the airway to react to stimuli or triggers to cause an asthma attack. Bronchoconstriction is a narrowing of the airways that causes airflow obstruction. Possible triggers are listed in Table 25.1. One of the most common trigger factors is the allergen found in the faeces of the house dust mite, which is almost universally present in bedding, carpets and soft furnishing. Pollen from grass (prevalent in June and July) can lead to seasonal asthma. The role of occupation in the development of asthma has become apparent with increased industrialisation. There are many causes of occupational asthma, and bronchial reactivity may persist for years after exposure to the trigger factor. Drug-induced asthma can be severe and the most common causes are  $\beta$ -blocker drugs and prostaglandin synthetase inhibitors. The administration of  $\beta$ -adrenoceptor blockers to a patient, even in the form of eye drops, can cause  $\beta_2$ -receptor

**Table 25.1** Examples of asthma triggers

Trigger	Examples
Allergens	Pollens, moulds, house dust mite, animals (dander, saliva and urine)
Industrial chemicals	Manufacture of, for example, isocyanate-containing paints, epoxy resins, aluminium, hair sprays, penicillins and cimetidine
Drugs	Aspirin, ibuprofen and other prostaglandin synthetase inhibitors, $\beta$ -adrenoceptor blockers
Foods	A rare cause but examples include nuts, fish, seafood, dairy products, food colouring, especially tartrazine, benzoic acid and sodium metabisulfite
Environmental pollutants	Traffic fumes, cigarette smoke, sulphur dioxide
Other industrial triggers	Wood or grain dust, colophony in solder, cotton, dust, grain weevils and mites
Miscellaneous	Cold air, exercise, hyperventilation, viral respiratory tract infections, emotion or stress, swimming pool chlorine

blockade and consequent bronchoconstriction. Selective  $\beta$ -adrenoceptor blockers are thought to pose slightly less risk, but as these lose their selectivity at higher doses, it is generally recommended that this group of drugs is avoided altogether in asthma patients. Aspirin and related non-steroidal anti-inflammatory drugs can cause severe bronchoconstriction in susceptible individuals. Aspirin inhibits the enzyme cyclo-oxygenase, which normally converts arachidonic acid to (bronchodilatory) prostaglandins. When this pathway is blocked, an alternative reaction predominates, leading to an increase in production of bronchoconstrictor (cys-) leukotrienes. Figures from differing studies vary, but between 2% and 20% of the adult asthma population are thought to be sensitive to aspirin.

## Pathophysiology

Asthma can be classified according to the underlying pattern of airway inflammation with the presence or absence of eosinophils in the airways (eosinophilic vs. non-eosinophilic). Traditionally patients are described as having 'extrinsic asthma' when an allergen is thought to be the cause of their asthma. This is more common in children with a history of atopy, where triggers, such as dust mite, cause IgE production. Other environmental factors are also important, such as exposure to rhinovirus during the first 3 years of life (Holgate et al., 2010). 'Intrinsic asthma' develops in adulthood, with symptoms triggered by non-allergenic factors such as a viral

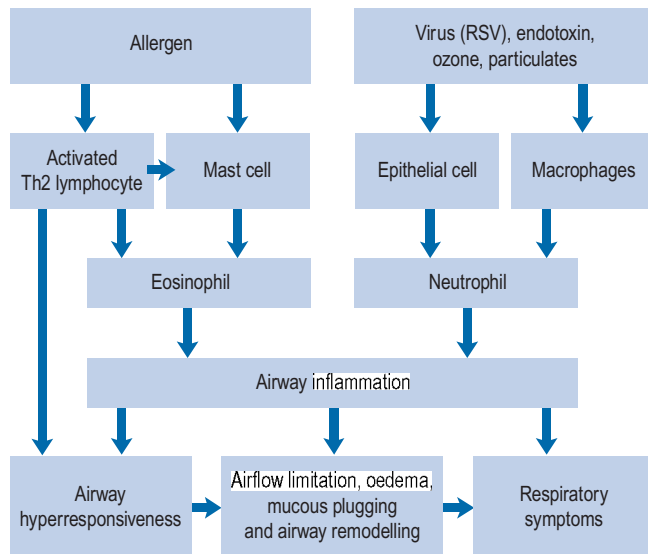
infection, irritants which cause epithelial damage and mucosal inflammation, emotional upset which mediates excess parasympathetic input or exercise which causes water and heat loss from the airways, triggering mediator release from mast cells. In practice, patients often have features of both types of asthma and the classification is unhelpful and oversimplifies the pathogenesis of asthma.

Mast cell components are released as a result of an IgE antibody-mediated reaction on the surface of the cell. Histamine and other mediators of inflammation are released from mast cells, for example, leukotrienes, prostaglandins, bradykinin, adenosine and prostaglandin-generating factor of anaphylaxis, as well as various chemotactic agents that attract eosinophils and neutrophils. Macrophages release prostaglandins, thromboxane and platelet-activating factor (PAF). PAF appears to sustain bronchial hyperreactivity and cause respiratory capillaries to leak plasma, which increases mucosal oedema. PAF also facilitates the accumulation of eosinophils within the airways, a characteristic pathological feature of asthma. Eosinophils release various inflammatory mediators such as leukotriene  $C_4$  ( $LTC_4$ ) and PAF. Epithelial damage results and thick viscous mucus is produced that causes further deterioration in lung function. These cell-derived mediators also play a role in causing marked hypertrophy and hyperplasia of bronchial smooth muscle (these structural changes are described as 'airway remodelling'), mucus gland hypertrophy leading to excessive mucus production and airway plugging, airway oedema, acute bronchoconstriction and impaired mucociliary clearance.

Mucus production is normally a defence mechanism, but in asthma patients, there is an increase in the size of bronchial glands and goblet cells that produce mucus. Mucus transport is dependent on its viscosity. If it is very thick, it plugs the airways, which also become blocked with epithelial and inflammatory cell debris. Mucociliary clearance is also decreased due to inflammation of epithelial cells. The environmental insults causing asthma are also thought to affect the structure and function of the airway epithelium. The exact role of these cytokines, cellular mediators and the interrelationships with each other and with the causative allergenic or non-allergenic mechanisms has, however, yet to be fully determined and may vary over time (Douwes et al., 2002; Holgate et al., 2010). Fig. 25.1 outlines the main cellular mechanisms involved.

## Clinical manifestations

Asthma can present in a number of ways. It may manifest as a persistent cough, but most commonly, it is described as recurrent episodes of difficulty in breathing (dyspnoea) associated with wheezing (a high-pitched noise due to turbulent airflow through a narrowed airway). Diagnosis is usually made from the clinical history confirmed by demonstration of reversible airflow obstruction and measures of lung function. The history of an asthma patient often includes the presence of atopy and allergic rhinitis in the close family. Symptoms of asthma are often intermittent, and the frequency and severity of an episode can vary from individual to individual. Between periods



**Fig. 25.1** Postulated cellular mechanisms involved in airway inflammation (adapted from Douwes et al., 2002).

of wheezing and breathlessness, patients may feel quite well. The absence of an improvement in ventilation, however, cannot rule out asthma, and in younger children, it is sometimes very difficult to perform lung function tests; in this case, diagnosis relies on subjective symptomatic improvement in response to bronchodilator therapy.

Acute severe asthma is a dangerous condition that requires hospitalisation and immediate emergency treatment. It occurs when bronchospasm has progressed to a state where the patient is breathless at rest and has a degree of cardiac stress. This is usually progressive and can build up over a number of hours or even days. The breathlessness, with a peak flow rate <math><100\text{ L/min}</math>, is so severe that the patient often cannot talk or lie down. Expiration is particularly difficult and prolonged as air is trapped beneath mucosal inflammation. The pulse rate can give an indication of severity; severe acute asthma can increase the pulse rate to more than 110 beats/min in adults. It is common to see hyperexpansion of the thoracic cavity and lowering of the diaphragm, which means that accessory respiratory muscles are required to try to inflate the chest. Breathing can become rapid (>30 breaths/min) and shallow, leading to low oxygen saturation ( $\text{SpO}_2 < 92\%$ ) with the patient becoming fatigued, cyanosed, confused and lethargic. The arterial carbon dioxide tension ( $\text{PaCO}_2$ ) is usually low in acute asthma. If it is high, it should respond quickly to emergency therapy. Hypercapnia (high  $\text{PaCO}_2$  level) that does not diminish is a more severe problem and indicates progression towards respiratory failure.

Some patients remain difficult to control with persistent symptoms and/or despite treatment at BTS/SIGN step 4 or 5. This is known as 'refractory' or 'difficult to treat' asthma. These patients must be carefully evaluated by a respiratory specialist; this will include confirming an accurate diagnosis of asthma, adherence to therapy and individual psychological factors.

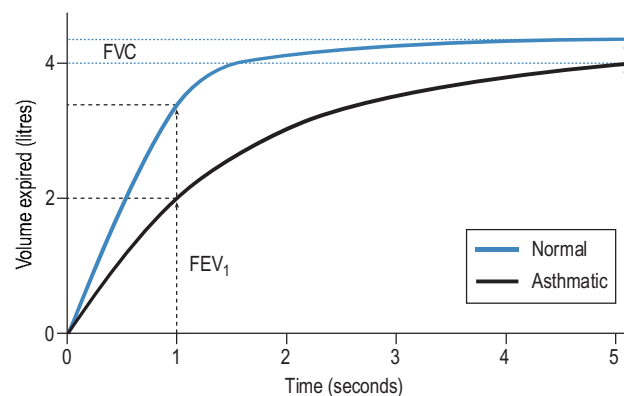
## Investigations

The function of the lungs can be measured to help diagnose and monitor various respiratory diseases. A series of routine tests has been developed to assess asthma as well as other respiratory diseases such as COPD.

The most useful test for abnormalities in airway function is the forced expiratory volume (FEV). This is measured by means of lung function assessment apparatus such as a spirometer. The patient inhales as deeply as possible and then exhales forcefully and completely into a mouthpiece connected to a spirometer. The  $\text{FEV}_1$  is a measure of the FEV in the first second of exhalation. The forced vital capacity (FVC) can also be measured, which is an assessment of the maximum volume of air exhaled with maximum effort after maximum inspiration. The  $\text{FEV}_1$  is usually expressed as a percentage of the total volume of air exhaled, reported as the  $\text{FEV}_1/\text{FVC}$  ratio. This ratio is a useful and highly reproducible measure of the capabilities of the lungs. Normal individuals can exhale at least 70% of their total capacity in 1 s. In obstructive lung disorders, such as asthma, the  $\text{FEV}_1$  is usually decreased, the FVC normal or slightly reduced and the  $\text{FEV}_1/\text{FVC}$  ratio decreased, usually <math><0.7</math> (Fig. 25.2).

A peak flow meter is a useful means of self-assessment for the patient. It gives slightly less reproducible results than the spirometer but has the advantage that the patient can do regular tests at home with a hand-held meter. The peak flow meter measures peak expiratory flow (PEF) rate, the maximum flow rate that can be forced during expiration. The PEF can be used to assess the improvement or deterioration in the disease as well as the effectiveness of treatment. For all three measurements ( $\text{FEV}_1$ , FVC and PEF), there are normal values with which the patient's results can be compared. However, these normal values vary with age, race, gender, height and weight. The measurement of  $\text{FEV}_1$ , FVC or PEF does not detect early deterioration of lung function such as bronchospasm and mucus plugging in the smaller airways.

The diagnosis of asthma can be confirmed by measuring the response to a bronchodilator or by examining a patient's day-to-day variation in PEF readings. A diurnal variability of 60 L/min (or more than 20%) is highly suggestive of asthma



**Fig. 25.2** Typical lung spirometry in normal subjects and asthma patients.

(GINA, 2009). However, individuals may not have airflow obstruction at the time of the test, so the absence of an improvement does not rule out asthma. In this situation, peak flow readings can be done at home with repeated pre- and post-bronchodilator readings taken at various times of the day.

## Treatment

As asthma involves inflammation and bronchoconstriction, treatment should be directed towards reducing inflammation and increasing bronchodilation. Treatment aims should include a lack of day and nighttime symptoms, no asthma exacerbations, no need for rescue medication, normal PEFs and no unwanted side effects from medication (BTS/SIGN, 2009; GINA, 2009). Anti-inflammatory drugs should be given to all but those with the mildest of symptoms. Other measures, such as avoidance of recognised trigger factors, may also contribute to the control of this disease. The lowest effective dose of drugs should be given to minimise short-term and long-term side effects. It should, however, always be remembered that asthma is a potentially life-threatening illness, is often undertreated and not all patients will achieve optimal control. Common therapeutic and practice problems encountered in the management of asthma are outlined in Box 25.1.

### Chronic asthma

The pharmacological management of asthma depends upon the frequency and severity of a patient's symptoms. Infrequent attacks can be managed by treating each attack when it occurs, but with more frequent attacks, preventive therapy needs to be used.

#### Box 25.1 Management of common practice problems

- Reducing exposure to trigger risk factors may help to improve asthma control.
- Successful management of asthma requires a partnership between the patient and the health care provider.
- Aim to give patients the ability to control their asthma by supporting guided self-management.
- Individualised action plans improve health outcomes, particularly in moderate to severe disease.
- Increased use of reliever medication is a warning of deterioration of asthma control.
- Assessment of asthma control is essential when deciding to step up or step down treatment.
- At each treatment review, inhaler technique and adherence to treatment should be checked.
- The main treatments for exacerbations of asthma include repeated  $\beta_2$ -agonists, early use of corticosteroids and oxygen to raise  $S_aO_2$  above 92%.
- Mild exacerbations (PEF reduction of <20%) can often be managed in community settings.
- After exacerbations, patients should be reviewed early to identify possible triggers and review the action plan.

$S_aO_2$ , arterial oxygen concentration.

The preferred route of administration of the agents used in the management of asthma is by inhalation. This allows the drugs to be delivered directly to the airways in smaller doses and with fewer side effects than if systemic routes were used. Inhaled bronchodilators also have a faster onset of action than when administered systemically and give better protection from bronchoconstriction.

Treatment of chronic asthma should be managed in a step-wise progression. This section concentrates on management in adults, as outlined in Fig. 25.3, but corresponding management steps for children are available (BTS/SIGN, 2009). Therapy is moved up the steps according to the severity of the patient's asthma symptoms and response to current treatment. When a patient has been stable for at least 3 months (GINA, 2009), therapy should be stepped back down; for example, by halving the inhaled corticosteroid (ICS) dose. International guidelines aim for management to achieve and maintain clinical control, which is defined in Table 25.2. A model for patient review and adjustment of therapy, based on assessment of asthma control, has been suggested (Crompton et al., 2006) and is shown in Fig. 25.4. To help in patient education, the terms used to describe the effects of asthma medication are similar across all manufacturers and sources of education. 'Reliever' is used for agents that give immediate relief of symptoms. Agents that act to reduce inflammation or give long-term bronchodilation are referred to as 'controllers' or 'preventers'.

### Reliever medication

**Short-acting  $\beta$ -adrenoceptor agonist bronchodilators.**  $\beta$ -Adrenoceptor agonists are the mainstay of asthma management. Salbutamol and terbutaline are selective  $\beta_2$ -agonists and have few  $\beta_1$ -mediated side effects such as cardiotoxicity.  $\beta_2$ -Receptors are, however, also present in myocardial tissue; cardiovascular stimulation resulting in tachycardia and palpitations is still the main dose-limiting toxicity with these agents when used in high dosage.

An inhaled  $\beta_2$ -agonist is the first-line agent in the management of asthma. This is used as required by the patient for the symptomatic relief of breathlessness and wheezing, for example, salbutamol 200  $\mu$ cg when required. This may be the only treatment necessary for those with infrequent symptoms. There is no advantage to regular administration.

**Additional bronchodilators.** Additional bronchodilators may be required if the above therapy does not adequately control symptoms (Tables 25.3 and 25.4).

**Inhaled anticholinergic agents.** These block muscarinic (M1, M2, M3) receptors in bronchial smooth muscle but are generally of little additional value in asthma management. Ipratropium has a slower onset of action than  $\beta_2$ -agonists but a longer duration of action. Anticholinergics may be helpful in patients who also have a degree of obstructive airways disease.

**Long acting  $\beta$ -adrenoreceptor agonist bronchodilators.** When low-dose inhaled steroids fail to control asthma symptoms adequately at step 3, long-acting  $\beta_2$ -agonists should be added instead of increasing the steroid dose. Symptom relief after a trial period, for example, 4–6 weeks, must then be assessed to

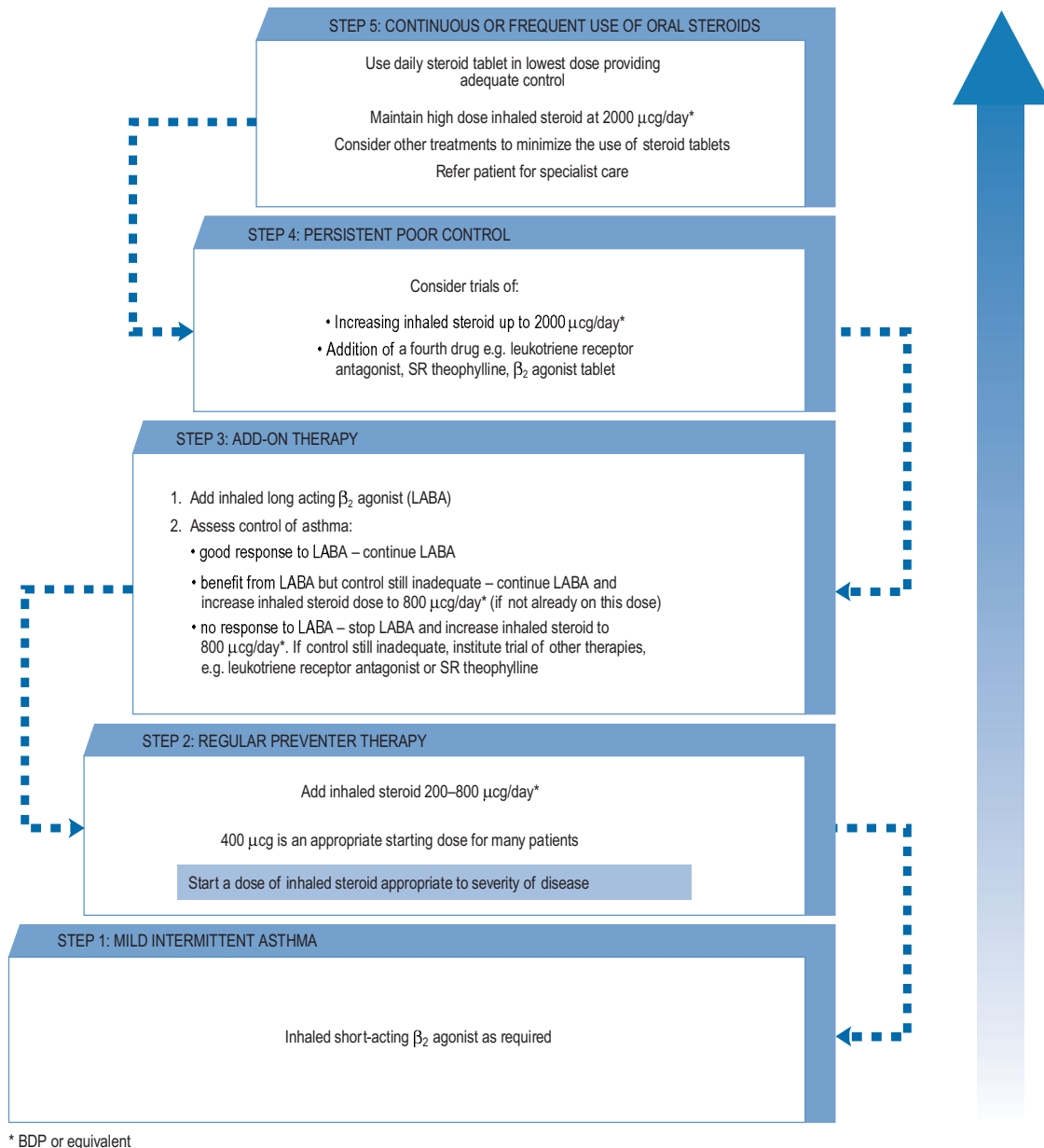
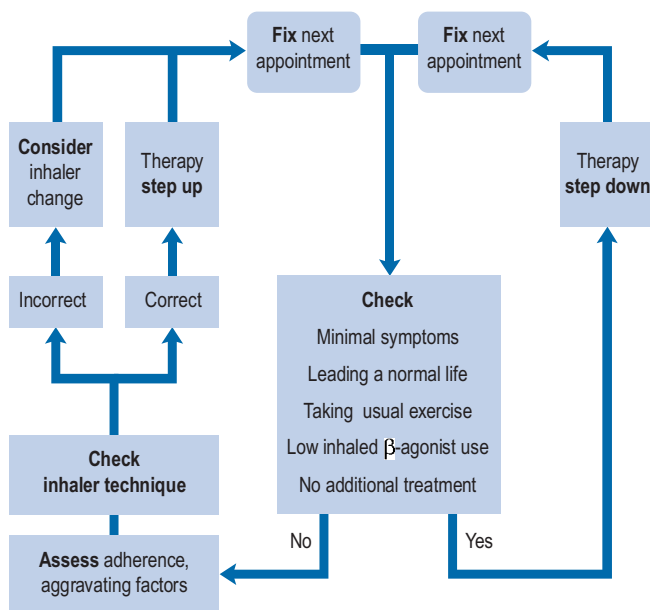


Fig. 25.3 Summary of stepwise management in adults (reproduced by permission of the BMJ Publishing Group, from BTS/SIGN, 2009).

Table 25.2 Levels of asthma control (GINA, 2009)

Characteristic	Controlled all of the following	Partly controlled any measure present in any week	Uncontrolled
Daytime symptoms	Twice or less/week	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitation of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	Twice or less/week	More than twice/week	
Lung function (PEF or FEV <sub>1</sub> )	Normal	<80% predicted or personal best (if known)	

Any exacerbation should prompt a review of maintenance treatment to ensure that it is adequate.



**Fig. 25.4** Adjusting therapy to achieve asthma control (from Crompton et al., 2006 reproduced by permission. Copyright Elsevier publishing).

see if the LABA has been effective and whether further treatment needs to be added to or existing treatment changed.

Meta-analysis of LABA trials has shown a potential increase in asthma deaths of 1 death in 1000 patient-years of use, but this increased risk is lessened when used alongside ICSs (Saltpeper et al., 2006). Taking this evidence into account, it is advised that LABAs should

- only be added if regular use of standard-dose ICS has failed to control asthma adequately
- not be initiated in patients with rapidly deteriorating asthma
- be introduced at a low dose and the effect properly monitored before considering dose increase
- be discontinued in the absence of benefit
- be reviewed as appropriate; stepping down therapy should be considered when good long-term asthma control has been achieved (MHRA, 2008).

Combination ICS/LABA inhalers are available which may improve adherence compared to separate inhalers; as adherence to ICS is generally poor, using combination inhalers may ensure that the LABA is not used alone for variable periods of time.

A formoterol and budesonide combination inhaler can be given both as maintenance therapy and for symptomatic relief. Current trial evidence shows that this dosing method is an alternative at step 3 for adults who are poorly controlled on SABA and ICS, have experienced one or more severe exacerbations in the previous 12 months, or as an alternative to increasing the ICS dose to above 2 mg/day at step 4 (NPC, 2008).

**Oral bronchodilators.** Oral bronchodilators can also be added, for example, theophylline at steps 3–4 or  $\beta_2$ -agonists at step 4 for additional symptom control. Slow-release forms should be used, usually twice daily, although these can be used in a single night-time dose if nocturnal symptoms are troublesome.

Theophylline should be started at a dose of 400–500 mg/day in adults and, if required, increased after 7 days to 800–1000 mg/day. In children, higher doses may be required but this will be determined by the age of the child (see Chapter 10).

Theophylline has a narrow therapeutic index and its hepatic metabolism varies greatly between individuals. Theophylline clearance is affected by a variety of factors, including disease states and concurrent drug therapy. The dose used should, therefore, take into account these factors, which are listed in Table 25.5. Plasma levels may be taken after 3–4 days at the higher dose, and it has been normal practice to adjust the dose to keep the plasma level within a therapeutic window of 10–20 mg/L, although improvements in respiratory function are seen at levels as low as 5 mg/L in some patients. As the bronchodilating effects of theophylline are proportional to the log of the plasma concentrations, there is proportionally less bronchodilation as the plasma level increases. The mild side effects such as nausea and vomiting are seen at concentrations as low as 13 mg/L but are more common over 20 mg/L. Significant cardiac symptoms, tachycardia and persistent vomiting are usually seen at concentrations of 40 mg/L while severe CNS effects, such as seizures, have been seen at 30 mg/L but are more common above 50 mg/L.

Drug	Onset of action (min)	Peak action (min)	Duration of action (h)
Ipratropium	3–10	60–120	4–6
Formoterol	2–3		12
Salbutamol	5–15	60 <sup>a</sup>	4–6
Salmeterol	10–14	150 <sup>a</sup>	12 <sup>a</sup>
Terbutaline	5–30	60–120	3–6

<sup>a</sup>Approximate or median value.

**Table 25.4** Daily dose range for selected bronchodilators

Drug and route	Age and total daily dosage range			
<b>Aminophylline</b>				
Intravenous injection	Adult; 5 mg/kg (single dose)	1 month–18 years; 5 mg/kg (single dose) up to 500 mg maximum		
Intravenous infusion	16 years–adult; 500 mg/kg/h	9–16 years; 800 mg/kg/h	1 month–9 years; 1 mg/kg/h	
Oral	Child over 40 kg–adult; 225–450 mg m/r twice a day			
<b>Formoterol</b>				
Inhaled	6 years–adult; 12–24 µcg twice a day			
<b>Ipratropium bromide</b>				
Inhaled	12 years–adult; 20–40 µcg 3–4 times daily	6–12 years; 20–40 µcg 3 times daily	1 month–6 years; 20 µcg 3 times daily	
Nebulised for acute bronchospasm	Adult; 500 µcg repeated as necessary	6–12 years; 250–500 µcg repeated as necessary (max. 1 mg daily)	Under 5 years; 125–250 µcg repeated as necessary (max. 1 mg daily)	
<b>Salbutamol</b>				
Inhaled	5 years–adult; 200 µcg when required, up to 4 times a day	Child, 100 µcg when required, up to 4 times a day		
Nebulised for acute bronchospasm	Adult; 2.5–5 mg repeated as necessary	6–18 years; 2.5–5 mg repeated every 20–30 min if necessary	2–5 years; 2.5 mg repeated every 20–30 min if necessary	Under 2 years; 2.5 mg repeated every 20–30 min if necessary
<b>Salmeterol</b>				
Inhaled	12 years–adult; 50–100 µcg twice a day	4–12 years; 50 µcg twice a day	2–4 years; 25 µcg twice a day	
<b>Terbutaline</b>				
Inhaled	5 years–adult; 500 µcg when required, up to four times a day			
Nebulised for acute bronchospasm	Adult; 5–10 mg repeated as necessary	6–18 years; 5–10 mg repeated every 20–30 min if necessary	2–5 years; 5 mg repeated every 20–30 min if necessary	Under 2 years; 5 mg repeated every 20–30 min if necessary
<b>Theophylline</b>				
Oral	12 years–adult; 175–500 mg (m/r) twice a day	6–12 years; 175–250 mg (m/r) twice a day		

Differing brands of theophylline have differing bioavailabilities, so brands should not be interchanged.

**High-dose  $\beta_2$ -agonists.** High-dose  $\beta_2$ -agonists are only considered if conventional doses do not achieve adequate symptom control. Nebulised drugs such as salbutamol 2.5–5 mg per dose are given.

Terbutaline has been given by continuous subcutaneous infusion in the maintenance treatment of difficult to treat asthma.

#### Preventer medication

**Anti-inflammatory agents.** Regular anti-inflammatory treatment should be used for patients who are not controlled on a SABA alone (BTS/SIGN, 2009). Corticosteroids are the most

commonly used anti-inflammatory agents (Table 25.6), but others such as the cromones are available.

**Inhaled corticosteroids.** Corticosteroids suppress the chronic airway inflammation associated with asthma. At present, ICSs are the initial drugs of choice, with a starting dose for an adult of beclometasone or budesonide 400 µcg/day (or an equivalent) given in divided doses.

The threshold frequency of  $\beta_2$ -agonist use which prompts the start of ICSs has not been fully established but national guidance (BTS/SIGN, 2009) recommends considering ICS for patients with any of the following:

- Exacerbations of asthma in the past 2 years
- Using inhaled  $\beta_2$ -agonists three times a week or more
- Symptoms three times a week or more
- Waking one night a week with symptoms

**Table 25.5** Factors affecting theophylline clearance

Decreased clearance	Increased clearance
Congestive cardiac failure	Cigarette smoking
Cor pulmonale	Children 1–12 years
Chronic obstructive pulmonary disease	High-protein, low-carbohydrate diet
Viral pneumonia	Barbecued meat
Acute pulmonary oedema	Carbamazepine
Cirrhosis	Phenobarbital
Premature and term babies	Phenytoin
Elderly	Sulfinpyrazone
Obesity	
High-carbohydrate, low-protein diet	
Cimetidine	
Erythromycin	
Oral contraceptives	
Ciprofloxacin	
Propranolol	

If symptoms persist, the ICS dose is increased stepwise accordingly. The ICS dose should be reduced, if possible, once symptoms and PEF rates have improved and stabilised. If a patient's asthma cannot be controlled by the above ICS dose and the inhaler technique and adherence are adequate, the dose can be increased to a maximum of 1.5–2 mg a day.

All ICSs have dose-related side effects. Adrenal suppression occurs at around doses of >1500 µg/day of beclometasone in adults. In children, doses of 400 µg/day of beclometasone or more are associated with growth failure and adrenal suppression; children treated at these doses should be under the care of a specialist paediatrician. Oropharyngeal side effects such as candidiasis are also more common at higher doses (Box 25.2). Measures to minimise this can be tried, such as using a large-volume spacer device and rinsing the mouth

with water or brushing teeth after inhalation, but there is little evidence to confirm how effective these are.

**Cromones.** Inhaled sodium cromoglicate and nedocromil sodium are less effective than corticosteroids in asthma. Although rarely used, they may be possible alternatives if corticosteroids cannot be tolerated.

**Leukotriene receptor antagonists.** Two leukotriene receptor antagonists, montelukast and zafirlukast, are currently licensed in the UK. Leukotriene receptor antagonists are included in step 4 as add-on therapy for adult patients but are less effective than LABAs in controlling asthma when added to ICSs. If these agents are initiated, then a 4–6 week trial should be undertaken; if there is no improvement in control, the drug should be stopped. They seem to be of particular value in aspirin-induced asthma, possibly due to the role of leukotrienes in this form of asthma.

**Anti-IgE monoclonal antibodies.** The first of these, omalizumab, is used for the treatment of severe persistent IgE (30–1500 iu/mL)-mediated asthma as add-on therapy to existing optimised therapy in adults and individuals over 12 years of age who have severe unstable disease (NICE, 2007). Patient response should be measured and omalizumab discontinued after 16 weeks if no adequate response is seen.

**Oral corticosteroids.** Oral corticosteroids should only be used, at step 5, if symptom control cannot be achieved with maximum doses of inhaled bronchodilators and steroids. They should be given as a single morning dose to minimise adrenal suppression. Alternate-day dosing produces fewer side effects but is less effective in controlling asthma.

Short courses (of up to 3 weeks) of high-dose oral steroids, 40–50 mg daily, can be safely used during exacerbations of asthma.

**Steroid-sparing agents.** Immunosuppressive agents can be tried in an attempt to reduce a regular steroid dose. Methotrexate, ciclosporin and gold have been tried with varying

**Table 25.6** Inhaled corticosteroids used for the prophylaxis of asthma

Drug and age range	Total daily dosage range (MDI)	
	Standard dose	High dose
<b>Beclometasone dipropionate or budesonide<sup>a</sup></b>		
Adult	100–400 µg twice a day	400–1000 µg twice a day
12–18 years	100–400 µg twice a day	400–1000 µg twice a day
Under 12 years	100–200 µg twice a day	200–400 µg twice a day
<b>Ciclesonide</b>		
Adult	80 µg once daily	160 µg once daily
<b>Fluticasone</b>		
Adult	50–200 µg twice a day	400–1000 µg twice a day
12–18 years	50–200 µg twice a day	200–500 µg twice a day
4–12 years	50–100 µg twice a day	100–200 µg twice a day
<b>Mometasone</b>		
Adult	200–400 µg once daily	400 µg twice a day
12–18 years	200 µg twice a day	Up to 400 µg twice a day

<sup>a</sup>There are bioavailability differences between CFC-free steroid inhalers. Always check dosing for specific brands.



**Box 25.2** Adverse reactions associated with drugs used in the management of asthma **$\beta_2$ -Agonists**

- *By inhalation:* adverse drug reactions are uncommon
- *Nebulisation, orally or parenterally:* fine tremor (usually the hands), nervous tension, headache, peripheral vasodilation, tachycardia. The adverse reactions often diminish as tolerance develops with continued administration
- *High doses:* hypokalaemia, aggravation of angina

**Inhaled corticosteroids**

- Hoarseness, oral or pharyngeal candidiasis
- Adrenal suppression may occur with high doses, for example, beclometasone dipropionate above 1500 $\mu$ cg daily

**Oral corticosteroids**

- Prolonged use of these results in exaggeration of some of the normal physiological effects of steroids
- Mineralocorticoid effects include: hypertension, potassium loss, muscle weakness, and sodium and water retention. These effects are most notable with fludrocortisone, are significant with hydrocortisone, occur only slightly with prednisolone and methylprednisolone and are negligible with dexamethasone and betamethasone
- Glucocorticoid effects include: precipitation of diabetes, osteoporosis, development of a paranoid state, depression, euphoria, peptic ulceration, immunosuppression, Cushing's syndrome (moon face, striae and acne), growth suppression in children, worsening of infection, skin thinning, striae atrophicae, increased hair growth, perioral dermatitis and acne
- Adrenal suppression occurs with high doses and/or prolonged treatment. Steroid therapy must be gradually withdrawn in these patients to avoid precipitating an adrenal crisis of hypotension, weight loss, arthralgia and, sometimes, death

**Ipratropium bromide**

- Occasionally: dry mouth
- Precipitation of acute glaucoma with nebulised therapy, possibly worsened by co-administration of salbutamol. A mouthpiece should be used to minimise the exposure of the eyes to the nebulised drug
- Rarely: systemic anticholinergic effects such as urinary retention and constipation

**Methotrexate**

- Myelosuppression, mucositis and, rarely, pneumonitis

**Nedocromil sodium**

- Mild and transient nausea, coughing, transient bronchospasm, throat irritation, headache and a bitter taste

**Sodium cromoglicate**

- Coughing, transient bronchospasm and throat irritation due to inhalation of the powder

**Theophylline**

- Although about 5% of the population experience minor adverse effects (nausea, diarrhoea, nervousness and headache), increasing the plasma concentration results in more serious effects. The following is a guide to the plasma levels at which the adverse reactions usually occur:
  - Above 20mg/L: persistent vomiting, insomnia, gastro-intestinal bleeding, cardiac arrhythmias
  - Above 35mg/L: hyperglycaemia, hypotension, more serious cardiac arrhythmias, convulsions, permanent brain damage and death
- Individual patients may suffer these effects at plasma levels other than those quoted, for example, convulsions have occurred in patients at 25mg/L

**Leukotriene receptor antagonists**

- Abdominal pain, headache, diarrhoea, dizziness, upper respiratory tract infections. Rarely: acute hepatitis (associated with zafirlukast), Churg–Strauss syndrome

success. All have potentially toxic side effects and need to be closely monitored.

**Acute severe asthma**

The management of acute asthma depends on the severity of the attack and its response to treatment, as well as an appreciation of the patient's past history and present treatment. If an acute attack becomes persistent and difficult to treat, it is known as acute severe asthma. The aims of treatment are to prevent any deterioration in the patient's condition and hasten recovery.

**Prevention.** The ideal way of treating an acute attack is to empower patients to recognise when their condition is

deteriorating so they can initiate treatment to prevent the attack becoming severe. This can be achieved with an individualised self-management plan.

The dose of inhaled  $\beta_2$ -agonist should be increased, and a short course of oral steroids commenced, for example, prednisolone at a dose of 40–50mg every morning for 1 week. The dose of ICS is often also increased, but there is limited evidence to support this.

If the condition deteriorates further, hospital admission may become necessary. This could be a self-referral from the patient, responding to criteria drawn up by the doctor, such as their PEF falling below 50% of their usual best. The education of patients and their relatives in the management of

acute attacks should always stress the prompt initiation of further treatment and early referral.

**Immediate management.** The immediate treatment of acute severe asthma should take place in the patient's home if a moderate attack. Admission to hospital is considered if PEF

drops below 50% predicted or normal, or the patient cannot complete sentences in one breath or is too breathless to talk, or if life-threatening features are present. A suggested treatment protocol for management in hospital is outlined in Fig. 25.5.

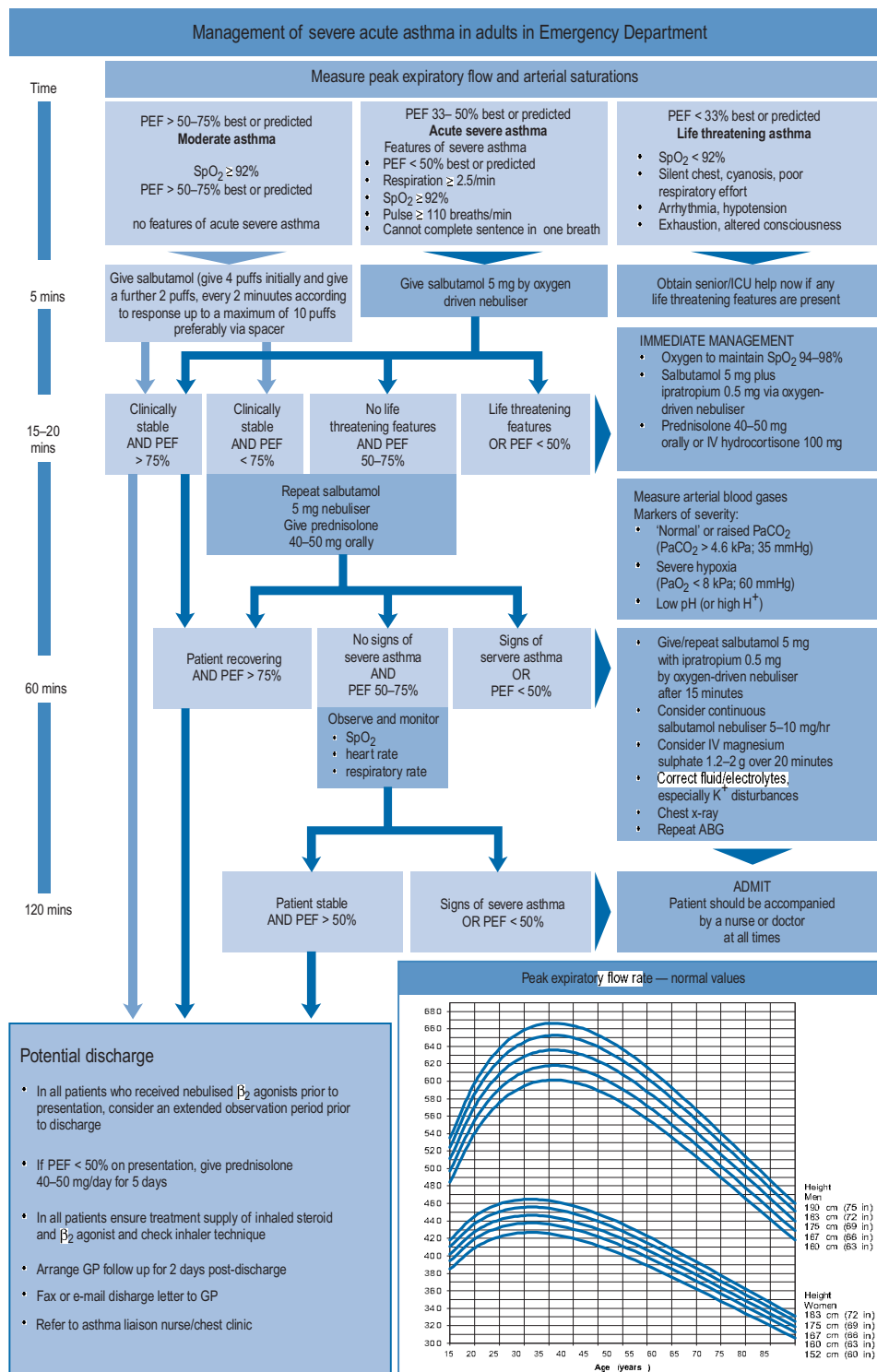


Fig. 25.5 Management of acute severe asthma in adults in hospital reproduced by permission of the Scottish Intercollegiate Guidelines Network from BTS/SIGN, 2009.

Oxygen is administered to achieve an oxygen saturation of 92% or more. A  $\beta_2$ -agonist is administered by metered dose inhaler (MDI) with a spacer attachment (4 puffs, then 2 puffs every 2 min until 10 mg or symptom relief) as there is no demonstrable difference between this and using a nebuliser. With more severe symptoms, or during an admission to hospital, nebulisers are used because they permit a high dose (10–20 times the dose of a MDI) and they require no co-ordination on the part of the patient between inspiration and actuation, which is helpful in those distressed. Patients undergoing an acute attack often have an inspiratory rate that is too low to use an MDI effectively.

Corticosteroids are also given in the acute attack; oral prednisolone (40–50 mg daily, for 5 days). Intravenous hydrocortisone (100 mg) should only be required if the patient cannot take oral medication. This reduces and prevents the inflammation that causes oedema and hypersecretion of mucus and hence helps to relieve the resultant smooth muscle spasm. The clinical response to both oral and parenteral steroids has an onset at 1–2 h with a peak effect at 6–8 h. If life-threatening features are present, such as cyanosis, bradycardia, confusion, exhaustion or unconsciousness, higher dose bronchodilators are used: nebulised salbutamol 5 mg with ipratropium bromide 500  $\mu$ g, repeated after 15 min; with subsequent consideration to continuous nebulisation of salbutamol at 5–10 mg/h. The addition of an anticholinergic such as ipratropium often gives a response that is greater than that of the two agents used alone.

Intravenous aminophylline can be given with a bolus dose of 250 mg over 30 min, followed by a continuous infusion of 500  $\mu$ g/kg/h. The bolus should be omitted if the patient is known to take oral theophylline or aminophylline. The choice between intravenous aminophylline and  $\beta_2$ -agonist depends on concurrent therapy and side effect profiles. The dose of intravenous aminophylline used must also take into account recent theophylline therapy in addition to other factors (Table 25.7). Serious toxicity can occur with parenteral aminophylline and patients must be carefully monitored for nausea and vomiting, the most common early signs of toxicity.

**Table 25.7** Intravenous aminophylline dosing in acute severe asthma

	Aminophylline dose	Patient characteristics
Loading dose	5 mg/kg over 20–30 min	Adults and children
	3 mg/kg over 10–15 min	Previous theophylline therapy (although some authorities do not use a loading dose in these patients)
Maintenance dose	500 $\mu$ g/kg/h 700 $\mu$ g/kg/h	Non-smoking adults Children under 12 or smokers
	200 $\mu$ g/kg/h	Cardiac failure, liver impairment, pneumonia

If the aminophylline infusion is continued for more than 24 h, the plasma theophylline concentration may be measured to guide any necessary alteration in infusion rate in order to maintain the level in the optimum range of 10–20 mg/L.

Intravenous magnesium sulphate, 1.2–2 g as a 20-min infusion, has been shown to help in some patients who have not had a good response to initial treatment. There is, however, no evidence to support repeated dosing regardless of therapeutic outcome.

Further deterioration in condition may require assisted mechanical ventilation on an intensive care unit. Regular monitoring of arterial blood gases and oxygen saturation is performed to help detect any deterioration in condition.

Antibiotics are only indicated where there is evidence of a bacterial infection.

**Ongoing management.** The subsequent management of acute severe asthma depends on the patient's clinical response. All patients should be monitored throughout their treatment with objective measures of their PEFs before and after bronchodilator treatment and with continual monitoring of their arterial blood gas concentrations to ensure adequate oxygen is being given.

As the patient responds to treatment, infusions can be stopped and other treatment changed or tailed off as described above. As improvement continues, an inhaled  $\beta_2$ -agonist is substituted for the nebulised form and the oral corticosteroids stopped or reduced to a maintenance dose if clinically necessary. Throughout the treatment programme, potential drug interactions should be anticipated and managed appropriately (Table 25.8).

All patients should have a follow-up after an acute attack with symptoms monitored, reasons for admission addressed and inhaler technique checked. A self-management plan should be drawn up and discussed with each patient.

## Patient care

The correct use of drugs and the education of patients are the cornerstones of asthma management. There are three main steps in the education of the asthmatic patient.

1. The patient should have an understanding of the action of each of the medicines they use.
2. The appropriate choice of inhalation device(s) should be made and the patient educated to use them correctly.
3. An individualised action (self-management) plan should be developed for each patient.

All members of the health care team should provide education and support for the asthmatic patient at regular intervals. The need for each patient to understand their asthma and its management must be balanced against the dangers of overwhelming the patient with information, particularly when the asthma has been newly diagnosed. To try to overcome this, a 'ladder of asthma knowledge' has been proposed. Patients are counseled in a gradual manner, each session adding to the previous one in content and reinforcing existing knowledge (Box 25.3).

**Table 25.8** Common clinically significant interactions with drugs used in the management of asthma

Drug	Interacting drug	Probable mechanism and clinical result
$\beta_2$ -Agonists	Methyldopa	Acute hypotension possible with $\beta_2$ -agonist infusions
Corticosteroids	Anticoagulants	High-dose steroids enhance anticoagulant effect of coumarins
	Antifungals	Metabolism of steroids possibly affected by antifungal agents
	Barbiturates	Accelerates steroid metabolism
	$\beta_2$ -Agonists	Increased risk of hypokalaemia with high doses
	Carbamazepine	Reduced steroid effect due to increased metabolism
	Ciclosporin	Increases plasma concentration of prednisolone
	Methotrexate	Increased risk of haematological toxicity
	Phenytoin	Reduced steroid effect due to increased metabolism
Rifampicin	Reduced steroid effect due to increased metabolism	
Theophylline	Azithromycin	May increase theophylline plasma levels
	$\beta_2$ -Agonists (high dose)	Increased risk of hypokalaemia
	Carbamazepine	Induction of theophylline metabolism resulting in decreased plasma levels
	Clarithromycin	Inhibition of theophylline metabolism resulting in increased plasma levels
	Cimetidine	Inhibition of theophylline metabolism resulting in increased plasma levels
	Ciprofloxacin	Increased plasma concentration. Possible risk of convulsions
	Diltiazem	Increased theophylline plasma levels
	Erythromycin (oral)	Inhibition of theophylline metabolism resulting in increased plasma levels
	Fluconazole	Possible increase in theophylline plasma level
	Dihydropyridine	
	calcium antagonists	May increase theophylline plasma levels
	Fluvoxamine	Increased theophylline plasma levels, halve theophylline dose
	Isoniazid	May increase theophylline plasma levels
	Ketoconazole	Possible increase in theophylline plasma level
	Lithium carbonate	Reducing plasma lithium concentrations as theophylline enhances lithium renal clearance
	Norfloxacin	Increased plasma concentration. Possible risk of convulsions
	Phenytoin	Plasma concentrations of theophylline and phenytoin both reduced
	Primidone	Induction of theophylline metabolism resulting in decreased plasma levels
	Rifampicin	Induction of theophylline metabolism resulting in decreased plasma levels
	Ritonavir	Metabolism of theophylline increased
Smoking (tobacco)	Induction of theophylline metabolism resulting in decreased plasma levels	
St John's wort	Reduced theophylline plasma levels	
Verapamil	Increased theophylline plasma levels	

**Box 25.3** Ladder of asthma knowledge for patients

Step 1: Patient/carer understands what relief medication does, side effects which may occur, aims of treatment, what is happening to them and their chest. Education material is made available

Step 2: Patient/carer accepts and agrees about use of medication, importance of preventers and recognition of symptoms

Step 3: Patient/carer knows how to monitor PEF and symptoms, when to increase dose of inhaled steroids and contact their medical practice

Step 4: Patient/carer confident to manage own medication, increasing and decreasing dose using PEF or symptom monitoring, start oral steroids and attend their medical practice

**Knowledge**

Increasing the patients' knowledge about their asthma therapy is a necessary component of asthma management. However, education alone has not been shown to have a beneficial effect on morbidity. Education programmes must, therefore, also look at modifying their behaviour and attitude to asthma. Counselling should lead to increased patient confidence in

the ability to self-manage asthma, thereby decrease hospital admission rates and emergency visits by primary care doctors, increase adherence and improve quality of life.

Specific counselling on drug therapy should concentrate on three areas: drugs used to relieve symptoms, drugs used to prevent asthma attacks, and drugs which are given only as reserve treatment for severe attacks.

**Inhalation device**

The choice of a suitable inhalation device is vital in asthma management. The incorrect use of inhalers will lead to sub-optimal treatment. A review of inhaler technique studies has concluded that up to 50% of patients in Europe are unable to use their inhaler correctly (Crompton et al., 2006). There is no demonstrable difference in efficacy between the various devices available. Other factors, therefore, need to be considered when choosing the appropriate device, including the patient's age, severity of disease, manual dexterity, co-ordination and personal preference. The range of different devices available for the drugs commonly used in asthma is shown in Table 25.9.

**Table 25.9** Inhalation devices and spacer devices available

Drug	Type of inhaler device						
	Metered dose	Breath-actuated spacer for MDI	Single-dose spacer for MDI	Multiple-dose dry powder inhaler	Nebuliser dry powder inhaler	Large-volume	Small-volume
Salbutamol	✓	✓	✓	✓	✓	✓	✓
Ipratropium	✓		✓		✓		✓
Terbutaline				✓	✓		
Salmeterol	✓			✓			✓
Formoterol			✓				
Tiotropium <sup>a</sup>	✓ <sup>b</sup>		✓				
Beclometasone	✓	✓	✓	✓			✓
Budesonide	✓			✓	✓	✓	✓
Ciclesonide	✓						✓
Fluticasone	✓			✓	✓	✓	✓
Mometasone				✓			
Cromoglicic acid	✓	✓	✓		✓		✓
Nedocromil	✓						✓

<sup>a</sup>Only licensed for use in COPD.  
<sup>b</sup>Delivers a soft aerosol 'mist'.

### Metered dose aerosol inhalers

The pressurised MDI is the most widely prescribed inhalation device in the UK (Fig. 25.6). It usually contains a solution or suspension of active drug, with a typical particle size of 2–5 µm, in a liquefied propellant. Operation of the device releases a metered dose of the drug with a droplet size of 35–45 µm. The increased droplet size is due to the propellant, which evaporates when expelled from the inhaler. Inhalers have now been switched from chlorofluorocarbon (CFC) propellants to newer, non-CFC, hydrofluoroalkanes.

MDIs have the advantage of being multidose, small and widely available for most drugs used in asthma management. Their main disadvantage is that correct use requires a good technique. A particular problem for many patients is co-ordinating the beginning of inspiration with the actuation of the inhaler. Even when this is done correctly, MDIs only deliver about 10% of drug to the airways, with 80% deposited in the oropharynx. Corticosteroids administered by MDIs can cause dysphonia and oral candidiasis. The candidiasis can be minimised either by advising patients to gargle with water after using the inhaler and to expel the water from the mouth afterwards, or by using a spacer device. Newer devices are utilising other mechanisms to produce an aerosol such as a soft mist inhaler (SMI) which may give benefits in lung deposition and ease of use.

**Fig. 25.6** Pressurised metered dose inhaler.

Age group	Drug group	First choice device	Second choice device
0–2 years	All	MDI + spacer + facemask	Nebuliser
3–4 years	All	MDI + spacer	Nebuliser or dry powder
5–15 years	Bronchodilators	MDI or dry	Powder or breath-actuated MDI
5–15 years	Corticosteroids	MDI + spacer	Dry powder or breath-actuated MDI

Younger children, in particular, find MDIs difficult to use and the addition of a spacer device can make this easier, allowing inhalation over several ambient breaths.

The correct technique for using MDIs is as follows:

1. MDIs have a mouthpiece dust cap which has to be removed before use (patients may fail to remove this). The cap must be replaced after use to prevent subsequent inhalation of foreign bodies.
2. The MDI must be vigorously shaken. This distributes the drug particles uniformly throughout the propellant (newer CFC-free inhalers may be solutions and not require shaking – see manufacturer's literature). The MDI must be held upright.
3. The patient should breathe out gently, but not fully.
4. The tongue should be placed on the floor of the mouth and the inhaler placed between the lips, which are then closed round the mouthpiece.
5. The patient should now start to breathe in slowly and deeply through the mouth.
6. The canister is pressed to release the dose while the patient continues to breathe in. This synchronisation of inspiration and actuation, so that there is a supporting stream of air to carry the drug to the lungs, is probably the most common point of failure in those with bad inhalation technique. Patients who are very short of breath, for example, during a severe asthma attack, find this particularly difficult.
7. The breath is held for at least 10 s. This allows the drug particles reaching the periphery of the lung to settle under gravity. Using this technique, about 15% of a dose may reach the lungs. Exhalation should be through the nose.
8. If a second dose is required, 30–60 s should elapse before repeating the inhalation procedure to allow the dosing chamber to re-fill.

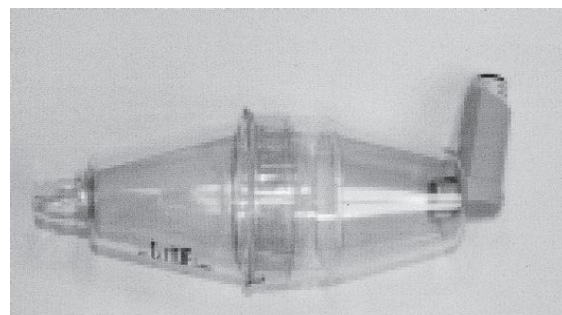
Studies indicate that personal tuition improves inhaler technique, particularly if regularly repeated. Other methods of instruction include videos (see <http://medguides.medicines.org.uk/demonstrations.aspx>), package inserts and information leaflets or booklets provided by organisations such as Asthma UK and the pharmaceutical industry. Regular patient review, at least annually, is recommended. This can be used as an opportunity to check technique, along with assessment of the ability to generate the appropriate inspiratory flow for the device (Broeders et al., 2009).

### Metered dose inhaler with a spacer extension

Extension devices allow greater evaporation of the propellant, so reducing particle size and velocity. This also reduces oropharyngeal deposition and potentially increases lung deposition. Oral candidiasis and dysphonia (impaired voice) from ICSs may also be reduced by using these devices. Spacers are useful for people who have poor co-ordination between inspiration and actuation and several types of spacer are available. In younger children, these offer advantages over MDIs alone with respect to adherence. Recommendations (see Table 25.10) have been published regarding device choice (NICE, 2000, 2002).

Large-volume (750 mL) spacers are available such as the Volumatic® (Fig. 25.7); these are manufacturer specific and have not been assessed or licensed for use with devices of other companies. These spacers have one-way valves that allow several inhalations of one dose from the spacer's chamber. No co-ordination is required between actuation of the MDI and inhalation. A large-volume spacer can be used instead of a nebuliser to deliver high doses of a  $\beta_2$ -agonist in acute severe asthma attacks. Disadvantages of these spacers include their large size, which renders them less portable, and their proven efficacy only with inhalers from the same manufacturer. Spacers should be washed regularly in warm, soapy water and left to drip dry without rinsing. Cloths should not be used for drying a spacer as this affects the antistatic coating of plastic spacers. All spacers should be replaced every 6–12 months. Facemasks are available for young children.

Small- and medium-volume spacer devices are available, either as an integral part of the design of some MDIs or as



**Fig. 25.7** Large-volume spacer (Volumatic®).

a separate device (Fig. 25.8). These spacers have also been used to compensate for poor inhaler technique in adults and reduce the oropharyngeal deposition of steroids. These are more convenient to carry around than the larger spacers. The published evidence of additional benefit from these devices in either increasing efficacy or decreasing adverse effects is more limited than with large volume spacers.

#### Breath-actuated metered dose inhalers

These MDIs are actuated automatically by inspiratory flow rates of about 22–36 L/min. A breath-actuated MDI is illustrated in Fig. 25.9. These eliminate the need for the correct co-ordination of inspiration and actuation but require priming before each actuation.



Fig. 25.8 Medium-volume spacer (Aerochamber Plus®).

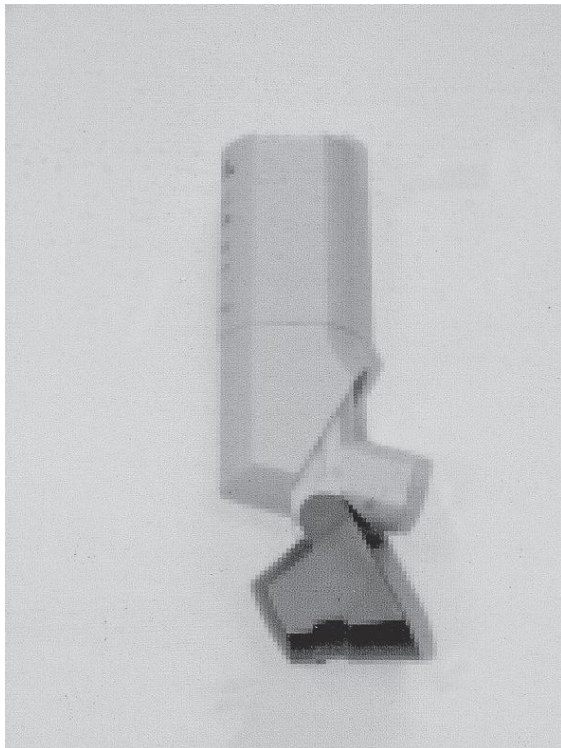


Fig. 25.9 Breath-actuated metered dose inhaler (Easi-breathe®).

#### Dry powder inhalers

Several types of dry powder inhalers (DPIs) are available. These are propellant free and are designed to be easier to use than conventional MDIs. They are useful for those who have difficulty co-ordinating an MDI and can be used by children as young as 4 years old. Table 25.10 sets out the recommendations for device choice in children.

DPIs are available as either single-dose or multiple-dose devices (Fig. 25.10). Single-dose devices pierce or break a gelatin capsule to release the contents and must be regularly cleaned to avoid powder clogging the device. Multiple-dose devices are preferred by many patients since they avoid having to reload for each dose. Care must be taken to hold these devices in the correct orientation to avoid the powder falling out of the device before inhalation. Patients commenced on DPIs are sometimes concerned at the absence of any taste or spray plume which they have become accustomed to when using an MDI; reassurance that this is perfectly normal and that correct use of the DPI (including a check that the device is not empty) will ensure that the required dose is delivered should overcome this problem.

#### Nebulisers

A nebuliser produces an aerosol by blowing air or oxygen through a solution to produce droplets of 5 µm or less in size. Nebulisers require little co-ordination from the patient as any drug is inhaled through a facemask or mouthpiece using normal tidal breathing. Only about 13%



Fig. 25.10 Multiple-dose dry powder inhaler (Turbohaler®).

of the dose used is deposited in the lungs, but because the doses used are higher than those used in other aerosol devices, patients will generally receive a higher dose than from an MDI. However, in mild and moderate exacerbations of asthma, no benefit has been shown over using 4–6 puffs of a MDI.

Nebulisers are useful in patients who are unable to use conventional inhalers, for example, children under 2 years old, patients with severe attacks of asthma unable to produce sufficient inspiratory effort and those lacking the co-ordination to use other inhalers. Nebulised bronchodilators can be used in acute severe asthma attacks, often avoiding the need for intravenous drugs.

Most of the short-acting  $\beta_2$ -agonists, as well as ipratropium bromide, fluticasone, budesonide and sodium cromoglicate, are available for nebulisation.

The safe and correct use of nebulisers requires careful counselling, especially if they are to be used in the home. The following points are critical for the correct use of a nebuliser.

1. Nebulisers should only be driven by compressed air or by oxygen at flow rates of at least 5–6 L/min to ensure that droplets of the correct size are produced.
2. To maximise nebulised drug, a minimum volume of 3–4 mL should be nebulised. This volume is required to reduce the amount of drug that is unavoidably left in the ‘dead-space’ (typically about 1 mL) at the end of nebulisation. This ‘dead space’ is less with newer nebulisers and no further dilution of commercial nebuliser solutions is used. Sodium chloride 0.9% must be used if solutions are diluted.
3. Most nebuliser chambers are disposable but will last 3–4 months when used by a patient at home. The chamber must be emptied after use, and each day, the chamber should be rinsed in hot water and dried by blowing air through the device. Several centres advocate that once a week the chamber

should be sterilised using 0.02% hypochlorite to prevent bacterial contamination; the chamber is then thoroughly rinsed to remove all traces of hypochlorite and then dried.

4. The nebuliser should be serviced at least once a year.

There are disadvantages with the use of nebulisers. Of particular concern is the overreliance on the nebuliser by some patients which results in a delay in seeking medical advice. The high doses of bronchodilators used can also increase the incidence of side effects, and these vary depending on the drug nebulised.

### Self-management programmes

Every individual with asthma should be considered for a self-management education programme. These programmes will contain structured education along with an individualised action plan. They aim to give the individual more confidence by involving them in the management of their own asthma. The individual should then be able to deal with any fluctuation in their condition and know when to seek medical advice. Personalised action plans have been shown to improve health outcomes in individuals with asthma (Gibson et al., 2002).

Key elements of an action plan include being able to monitor symptoms, measure peak flow, understand their medicine and how it should be used, and knowing how to deal with fluctuations in severity of asthma according to written guidance. Symptom diaries, management guidance cards and peak flow reading diary cards are available from organisations such as Asthma UK and pharmaceutical companies who manufacture asthma products.

An action plan can also include details of when to increase the dose of an inhaled steroid, when to take a short course of oral corticosteroids and when to self-refer to a general medical practitioner or local hospital (Table 25.11).

Peak flow	Example of symptoms	Action
>80% of personal best value	Intermittent or few symptoms	When required, $\beta_2$ -agonist for symptom relief, continue regular inhaler corticosteroid, consider reducing the dosage every 3 months if stable
61–80% of best	Waking at night Symptoms of a cold	Double dose of inhaled corticosteroid if taking <400 $\mu$ cg day BDP Start oral corticosteroid if taking >400 $\mu$ cg/day BDP
40–60% of best	Increasing breathlessness or using a $\beta_2$ -agonist every 2–3h	Start oral corticosteroid course. Contact a doctor
<40% of best	Severe attack Poor response to $\beta_2$ -agonist	Call emergency doctor or ambulance urgently

BDP, equivalent dose of beclometasone dipropionate.



## Case studies

### Case 25.1

Mr GT is 54 years old and has been diagnosed with asthma for 4 years. He is 180 cm tall and weighs 95 kg. He has recently been admitted to hospital with an acute exacerbation of his asthma, precipitated by a lower respiratory tract infection. During his admission, his steroid medication was altered from Qvar Easi-breathe® 100µcg twice daily to Symbicort 400/12 Turbohaler® 1 puff twice daily. He also takes Salbutamol Easi-breathe® inhaler 200µcg when required.

#### Questions

1. By how much has his ICSs dose been increased?
2. Should Mr GT be reviewed after discharge?
3. Would Mr GT benefit from self-management information and a personalised action plan?
4. Four months after his discharge, Mr GT has had no further exacerbations and his daily best PEF reading is around 520L/min; he has no limitations of activity because of his asthma and uses his salbutamol inhaler between two and three times a week. How can Mr GT's level of asthma control be determined?
5. You determine that Mr GT's asthma is now controlled. Could his therapy now be stepped down? If so, how should this be done?

#### Answers

1. Qvar® is a hydrofluoroalkane CFC-free inhaler with microfine particles of a mass median diameter of 1.1µm. Clinical studies show that adult patients require approximately half the dose of Qvar® to achieve the same degree of asthma control as with CFC-containing beclometasone inhalers. Care must always be taken when switching between ICS brands (see <http://www.mhra.gov.uk/>). Tables exist to help with determining equivalent doses (BTS/SIGN, 2009). Qvar® 200µcg daily is equivalent to 400µcg of other beclometasone/budesonide preparations, so Mr GT's ICS dose has been doubled.
2. He should be reviewed within 1 month of hospital discharge. This has been associated with a reduced risk of further acute episodes.
3. He would benefit from self-management information and a personalised action plan. The evidence of improved health outcomes for asthmatic patients is particularly good for those with moderate to severe disease and those who have had recent exacerbations.  
A personalised action plan should contain:
  - Advice about recognising loss of asthma control, as assessed by symptoms and PEF readings
  - The action to take if asthma deteriorates, including when and how to seek emergency help and when to commence a course of emergency oral steroids, which should be prescribed in advance.
4. Asthma control is usually assessed on the basis of clinical history, symptoms, inhaler usage and technique. An acute exacerbation is often indicative of poor control over a period of time.  
The level of asthma control for Mr GT can be determined by utilising tools such as the levels of asthma control in the GINA guidelines (GINA, 2009; Table 25.2) and the commonly used Royal College of Physicians, '3 questions':

- Have you had difficulty sleeping because of your asthma symptoms (including cough)?
- Have you had your usual asthma symptoms during the day (cough, wheeze, chest tightness or breathlessness)?
- Has your asthma interfered with your usual activities (e.g. housework, work/school, etc.)?

#### Management issues should also be discussed:

- Any issues of importance to the patient
- Inhaler technique must be checked, any deficiencies corrected, and if necessary a different device tried
- Adherence to prescribed medication should be assessed
- Mr GT has to be willing to try a step-down in his therapy. His ICS dose can be reduced slowly; a reduction of between 25% and 50% is usually tried every 3 months. A reduction to Symbicort® 200/6 1 puff twice daily could be attempted at this stage. The potential for worsening symptoms and the increased risk of exacerbation should be explained when step-down is attempted, particularly as the LABA dose is also being reduced. Opportunity should be taken to also promote general lifestyle advice:
  - Mr GT's body mass index is 29.3 and he is classed as overweight. He should be advised that a healthy diet and regular exercise will help with weight reduction and improve asthma control
  - Offer stop smoking advice if relevant
  - Advise him to avoid exposure to tobacco smoke
  - Provide allergen avoidance advice

Mr GT should be asked to keep twice daily PEF readings and a symptom diary. He will need to be reviewed again in 3 months unless symptoms deteriorate before then. Mr GT should be advised to consider increasing his medication again if his asthma deteriorates; his action plan can be adjusted accordingly.

### Case 25.2

Mrs LJ is 32 years old and was recently diagnosed on hospital admission with breathlessness following exposure to cold air. You are conducting a follow-up review after her hospital admission.

#### Questions

1. What advice should you cover in your consultation with Mrs LJ? Mrs LJ tells you that she has a cat and wonders if this could be affecting her asthma.
2. What information can you give Mrs LJ on allergen avoidance?

#### Answers

1. Effective management of asthma requires a partnership between the patient and the health care professionals involved in providing the care. The aim is to enable and empower the patient to gain the confidence, skills and knowledge to take a major role in the management of their asthma (GINA, 2009). Open-ended questions such as 'If we could make one thing better about your asthma what would it be?' may help to elicit a patient-centred agenda (BTS/SIGN, 2009). Topics that should be covered in this and subsequent consultations include:
  - Nature of the disease
  - Nature of the treatment
  - Identification of areas where the patient most wants treatment to have effect
  - How to use the treatment, particularly inhaler technique. Websites with video instruction, such as <http://www.medicines.org.uk/Guides/Pages/how-to-use-your-inhaler-videos> can be used to reinforce verbal instruction and demonstration.

- Develop self-monitoring/self-assessment skills
- Negotiate a personalised action plan in light of identified patient goals
- Recognise and manage acute exacerbations
- Appropriate allergen or trigger avoidance, for example, smoking, pollen, exercise, air pollution and stress
- Ensure Mrs LJ has received a current influenza vaccination

Practical information and treatment plans should be reinforced with written instruction; this can also be from patient support groups such as Asthma UK <http://www.asthma.org.uk/>. Every subsequent consultation with any health care professional should be an opportunity to review reinforce and extend both knowledge and skills.

2. There is no doubt that increased allergen exposure in sensitised individuals is associated with an increase in asthma symptoms, bronchial hyperresponsiveness and deterioration in lung function (BTS/SIGN, 2009); this includes animal allergens. However, the removal of cats from the home has not been shown to always benefit individuals with asthma. The reduction of exposure to other allergens, such as house dust mite, may also be considered for their potential effect on asthma symptoms. There is no evidence for the effectiveness of dust mite reduction strategies (Getzsche and Johansen, 2008).

If Mrs LJ wishes to try and reduce the burden of allergens in her home, then the following can be considered:

- Complete barrier bed-covering systems
- Remove carpets
- Remove soft toys from beds for children
- High temperature washing of bed linen
- Use acaricides on soft furnishings
- Ensure good ventilation with or without dehumidification
- Use a high-efficiency vacuum cleaner with an inbuilt air filter to reduce cat allergens.

If these measures provide no benefit to asthma symptoms or quality of life after a trial of a few months, they should be stopped.

### Case 25.3

**Mr KM is a 49-year-old man who has been diagnosed with asthma since childhood. He also suffers from allergic rhinitis with symptoms following exposure to grass pollen in the early summer. He is also allergic to cats. Over the past 2 years his asthma has been steadily deteriorating with a marked reduction in his ability to walk without becoming breathless. He now experiences daily symptoms and is woken up at night several times a week with shortness of breath which is temporarily relieved using a salbutamol inhaler. His current medication is:**

**Salbutamol DPI 200µcg when required (currently using three or four times every day)**

**Seretide-250® evohaler® 2 puffs twice daily  
Montelukast 10 mg at night  
Aminophylline m/r (Phyllocontin®) 450 mg twice daily**  
**He has had five exacerbations in the past 18 months, requiring hospitalisation. His last admission was 1 month ago with a severe exacerbation requiring a short period of ventilation support. He was discharged with a course of prednisolone 40 mg daily for 14 days but has had to continue taking prednisolone and currently takes 10 mg daily.**

### Questions

1. At which step of the BTS/SIGN guidelines is Mr KM, and what is his likely diagnosis?
2. What should be the next step in his management?
3. Is there a link between asthma and allergic rhinitis?
4. Mr KM has a positive skin prick test for animal dander and his IgE titre measures 425 IU/L. Is Mr KM suitable for treatment for omalizumab and, if so, for how long should this be given?

### Answers

1. He is at step 5, with uncontrolled asthma despite taking 1000µcg of inhaled fluticasone daily (equivalent to 2000µcg of beclometasone), a LABA, and three other medications, including oral steroids. It is likely that Mr KM has 'difficult to treat' asthma.
2. Mr KM should be referred to a respiratory specialist. He requires careful assessment which will include:
  - Confirmation or verification of the diagnosis of asthma, including asthma subsets such as steroid-resistant asthma (PEF increase less than 15% after 2 weeks of steroids), psychosocial asthma, premenstrual asthma, aspirin-induced asthma, rhinitis, occupational asthma, allergic bronchopulmonary aspergillosis
  - Identification of preventable causes of persistent symptoms
  - A review of inhaler technique
  - An assessment of adherence to treatment. A significant proportion of patients who may be considered difficult to treat are non-adherent with their corticosteroid therapy. The number of ICS and SABA inhalers dispensed per year can be an indicative measure of non-adherence
  - IgE titre.
3. Allergic rhinitis co-exists with asthma in the majority of patients. The rhinitis should be treated with intranasal steroids as this has been demonstrated to improve asthma morbidity.
4. Mr KM meets the criteria for omalizumab to be given. Omalizumab takes between 12 and 16 weeks to demonstrate effectiveness. Mr KM should be reviewed at 16 weeks and omalizumab only continued if there is a marked improvement in symptoms.

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